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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/501,171	02/09/2000	Peter George-Hyslop	1034/1F811-US1	3487

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EXAMINER	
TURNER, SHARON L	
ART UNIT	**PAPER NUMBER**
1647	13

DATE MAILED: 05/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/501,171	ST. George Hyslop
Examiner	**Art Unit**
Sharon L. Turner, Ph.D.	1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 3-12-02

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 2-13 is/are pending in the applica

4a) Of the above, claim(s) 6-13 is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 2-5 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims 2-13 are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Response to Amendment

1. The amendment filed 3-12-02 has been entered into the record and has been fully considered. Claim 1 is canceled. Claims 2-13 are pending.

2. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

3. As a result of applicants amendment, all rejections not reiterated herein have been withdrawn by the examiner.

Election/Restriction

4. Applicant's election without traverse of Group I, claims 1-5 in Paper No. 9 is acknowledged.

5. Claims 6-13 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 9.

6. This application contains claims 6-13 drawn to an invention nonelected **without** traverse in Paper No. 9. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to

make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 2 and 4-5 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Applicants argue that the new terms are supported by the specification at p. 4, lines 7-10 and p. 5, lines 17-24 and that the combination of structural and functional features provided adequately describe the invention.

Applicants arguments filed 3-12-02 with respect to the new claims have been fully considered but are not persuasive. The claims recite human neural plakophilin related armadillo proteins comprising C-terminal armadillo repeats and which are selected from full length hNPRAP peptides and a biologically active hNPRAP analogue. Applicants point to support for such recitations at p. 4, lines 7-10 and p. 5, lines 17-24. It is further noted that of such other proteins with armadillo repeat are p0071 and β-catenin proteins as noted at p. 4, lines 25-27. "hNPRAP" however, is defined at p. 5, lines 16-28 as a, "biologically active polypeptide that contains a sequence of hNPRAP," (presumably a portion of SEQ ID NO:4), "that mediates its nerve cell growth stimulating activity, e.g., the armadillo repeats. Thus, hNPRAP includes full-length (naturally occurring hNPRAP, as well as biologically active analogues thereof."

The specification discloses SEQ ID NO: 4 which corresponds to a full length hNPRAP peptide. This SEQ ID NOs meet the written description provisions of 35 USC 112, first

paragraph. However, the claims are directed to or encompass partial peptides which merely comprise a C-terminal armadillo-like repeats and which are biologically active hNPRAP analogues. While the specification describes that p0071 and β-catenin proteins contain a C-terminal armadillo-like repeat and describe that an analogue includes murine hNPRAP homologues of SEQ ID NO's: 5 and 6, the specification fails to describe that which constitutes the structural requirements of "a hNPRAP peptide comprising a C-terminal armadillo-like repeat" or that which constitutes the structural requirements of a "biologically active hNPRAP analogue." Furthermore, there is no defining functional requirement for that which constitutes a C-terminal armadillo-like repeat peptide (it is noted that the peptides are recognized to interact with presenilins or other proteins at p. 4, lines 23-27) or that which is a biologically active hNPRAP, although the claim requires that whatever the structure of the peptides are they are required to be present in an amount effective to provide nerve growth stimulatory activity (claim 2), neuronal regeneration (claim 4) and synapse formation (claim 5). Thus, the claims are deemed generic recitations which encompass corresponding sequences from other species, mutated sequences, allelic variants, splice variants, partial peptides and sequences with various degrees of identity, similarity or homology and differing degrees of function. However, none of these generic sequences meets the written description provision of 35 USC 112, first paragraph.

A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id at 1170, 25 USPQ2d at 1606."

While the instant products are not to a DNA or a cDNA as claimed, but to particular peptides, an analogy to the extent of products in general is still possible. A description of a genus may be achieved by means of a recitation of a representative number species, falling within the scope of the genus, by a recitation of structural features common to the genus, or by a correlation between structural and functional features which describe the invention such that the artisan is apprised of that which is the invention and that the inventor was in fact in possession of

the genus claimed. However, as noted above, while the instant specification discloses particular full length peptides which are disclosed as containing a C-terminal armadillo-like repeats (p0071 and β-catenin), as being full length hNPRAP molecules (SEQ ID NO:4) or analogues thereof (SEQ ID NO:5 or 6), the specification fails to disclose the structural constraints for those alternative and partial peptide sequences encompassed by the claims which reasonably correlate to the provision of neuronal growth, regeneration or synapse formation.

The artisan cannot discern the degree of homology which is required amongst the peptides, the required residues, or lengths whereby maintenance of function is retained. While the peptides may be loosely described by homology, protein function cannot be reliably predicted from protein sequence homology, see in particular Skolnick et al., Trends in Biotech., 18(1):34-39, 2000. Given the unpredictability of homology comparisons, and the fact that the specification fails to provide objective evidence to the breadth in structure which provides for the function of providing neuronal outgrowth, regeneration and synapse formation, thereby indicating the materials which indeed are species of the claimed genus, it cannot be established that a representative number of species have been disclosed to support the genus claim encompassing an extensive number of deletion, insertion and substitution variants. There is no proposed structure or consensus sequence definitive of the genus and the prior art does not provide compensatory structural or correlative teachings to enable one of skill in the art to identify the polypeptides encompassed by the claims.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that, "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is for purposes of the 'written description' inquiry, whatever is now claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed amino acid sequences and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The specific nucleic and amino acids are required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Therefore, the full breadth of the claims as encompassed by hNPRAP, C-terminal armadillo-like repeats and biologically active hNPRAP analogues fail to meet the written description provision of 35 USC 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

9. Claims 2-5 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants argue with respect to the new claims that the specification at p. 3, lines 6-15, p. 4, lines 11-16, p. 5, lines 16-24, p. 6, lines 1-8 and p. 7, lines 24 to p. 8, line 2 support the enablement within the skill in the art for the claimed invention and that any experimentation required would not be undue. Applicants argue that Skolnick is not particularly relevant to the art of nerve growth and that the non-enabled embodiments are not of interest.

Applicant's arguments filed 3-12-02 have been fully considered but are not persuasive. The specifications disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without undue experimentation. The factors relevant to this discussion include the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims.

The specification states at p. 4, lines 11-16 that "over-expression of hNPRAP, or functional derivatives thereof containing one or more armadillo repeats, causes the development of numerous long, dendritic processes which typically terminate upon distantly located cells," and that "the hNPRAP induced cellular extensions are highly similar to the axonal sprouting seen during neuronal regeneration and synapse formation." Yet, the specification fails to teach those cell types which exhibit this response upon contact with hNPRAP (i.e., fails to teach that

neuronal cells respond) and fails to show any exemplary evidence of neuronal regeneration or synapse formation using any disclosed peptide as claimed. As noted by Jackowski et al., Br. J. of Neurosurg., 9:303-317, 1995, neuronal cells and especially CNS neuronal cells differ from other cell types as CNS neurons are inhibited in regenerative capacity. Thus, the specification fails to evidence the claimed effects with any disclosed hNPRAP peptide, analogue thereof or peptide comprising a C-terminal armadillo-like repeat in stimulating growth of nerve cells, neuronal regeneration or synapse formation.

Further, the examiner notes that the observed effects noted at p. 4, lines 11-16 in the specification are generically displayed by a multitude of cells under various conditions, see in particular McDonald et al., Annals of the Rheumatic Diseases 1988 March, 47(3):232-40, Tanaka-Matakatsu et al., 1996 Dec., 122(12):3697-705, and Stamatoglou et al., Exp. Cell Res., 1992 Jan, 198(1):179-82, and that the noted effects in response to hNPRAP are not distinct among neuronal cells. Thus, the literature does not support a conclusion that the hNPRAP molecule is any more effective in promoting nerve cell growth, neuronal regeneration or synapse formation than for any of the other art noted effects including dendritic type outgrowth as indicated by filopodial extension in synoviocytes, drosophila trachea, or hepatocytes. Indeed it appears that the change in morphology noted by applicants specification may be an inconsequential event in the normal growth, differentiation, spreading or chemotaxis of any cell which as noted occurs in response to modification in microtubules and actin cytoskeleton.

Thus, based on the specifications limited observations the skilled artisan would fail to find the specifications evidence indicative of neuronal cell growth, regeneration or synapse formation as claimed as no exemplary evidence is provided and the references noted above would lead the artisan to doubt a necessary correlation between process outgrowth and neuronal outgrowth, neuronal regeneration and synapse formation.. It is additionally noted as set forth in Liuzzi et al., Neurosurg. Clin. Of N.Am., 2(1):31-42, 1991, that peripheral nerve regeneration and synapse formation is a process in which the relative success or failure of the event relies on the combined effects of a number of neuronal and non-neuronal events including the cellular and extracellular matrix, neurotrophic factors, the rate and efficiency of elongation and the specificity of target reinnervation amongst others, see in particular p. 31, paragraph 1. While such unpredictability is noted, the specification including at p. 3, lines 6-15, p. 4, lines 11-16, p. 5, lines 16-24, p. 6, lines 1-8, p. 7, lines 24 to p. 8, line 2, fail to teach a single exemplary embodiment where neurite growth is achieved with a hNPRAP of applicant's claims. Additionally, not a single prior art reference of record establishes neuronal outgrowth, neuronal regeneration or synapse formation with a hNPRAP molecule, a peptide comprising a C-terminal armadillo-like repeat or a biologically active hNPRAP analogue. Thus, the specification and prior art cumulatively fail to provide a single tangible exemplification which evidences that the generic sequences claimed bear any reasonable correlation to the provision of neuronal growth, regeneration or synapse formation which is reasonably produced or reasonably reproducible in any model system suggestive of providing for axonal growth, regeneration or synapse formation.

The specification states at p. 4, lines 23-27 that hNPRAP is known to interact with Presenilin I and II and that the domain of the PSI protein that interacts with hNPRAP has also been shown to interact with other proteins such as armadillo repeat proteins, p0071 and β-catenin, hNPRAP presumably being of such a family and merely requiring the armadillo repeats for the stimulation of neuronal regeneration and axon sprouting, specification p. 5, lines 16-28.

However, as taught by Paffenholz et al., (IDS) the plakoglobin/armidillo multigene family is made of a growing number of very different proteins which are divergent in function and independent in structure from each other, see in particular Introduction, p. 293-294. Paffenholz et al., clearly recognize armadillo repeat proteins, but fail to recognize neuronal growth as a function of such proteins. With this in mind, it is noted that applicants claims encompass peptides of undefined variable structure as encompassed by the generic recitation of hNPRAP, C-terminal armadillo-like repeats and analogues of hNPRAP. Yet, the skilled artisan readily recognizes the unpredictable nature of protein chemistry. As noted by Skolnick et al., Trends in Biotech., 18(1):34-39, 200 even in highly related protein families, structural modifications by even a single amino acid substitution may lead to functional changes in biological activity, see in particular Skolnick et al., Trends in Biotech., 18(1):34-39, 2000. Thus, the specification fails to teach the purported activities for the divergent molecules as encompassed by the claims.

Thus, without further undue experimentation the skilled artisan could not make and use the claimed invention without further undue experimentation to discover the invention which is claimed.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 2 and 4-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants argue with respect to the new claims that the metes and bounds include an armadillo-like repeat, nerve growth stimulating activity, hNPRAP of SEQ ID NO:4 and 6 or hNPRAP analogue with similar activity and is an hNPRAP modified by point mutation, amino acid substitution, addition or deletion or is a homologue and state that these modifications are well known in the art.

Applicants arguments filed 3-12-02 have been fully considered but are not persuasive. In contrast to applicants conclusion the specification at p. 5, lines 17-24 provides variable descriptions for that which can be "hNPRAP". As the descriptions are variable in and of themselves, the artisan has no guidance of which description to adopt to the meaning of "hNPRAP". Moreover as noted above a description of function fails to delineate the correlative structure which provides for that function. Applicant's arguments with respect to SEQ ID NO:6 appear to directly contradict the specification as the specification describes SEQ ID NO:6 as a murine analogue at p. 5, lines 22-23 but Applicant's arguments indicate that SEQ ID NO:6 is "hNPRAP" as is SEQ ID NO:4. Moreover, the specification provides no guidance for the structure which is a peptide comprising a C-terminal armadillo-like repeat other than p0071 and

β-catenin peptides contain it. Thus, the metes and bounds and structural constraints of hNPRAP, analogues and a C-terminal armidillo-like repeat cannot be readily discerned by the artisan based on the guidance in the specification and the prior art teachings.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 2 and 4-5 are rejected under 35 U.S.C. 102(b) as being anticipated by J. Regino Perez-Polo, US 5,475,088, Dec. 12, 1995.

Applicants argue that Perez-polo does not teach or suggest that his peptides are hNPRAP peptides or comprise a C-terminal armadillo-like repeat and thus as the aspects of the claimed invention are not implicitly or explicitly implied, the reference cannot be anticipatory.

Applicants arguments filed 3-12-02 have been fully considered but are not persuasive. While hNPRAP peptides, analogues and C-terminal armadillo-like peptides are indeterminate as noted above, Applicant's arguments make clear that modified peptides or mutants retaining the biological activity of stimulating neuronal growth, neuronal regeneration and synapse formation are within the scope of the invention. The question then becomes whether or not the peptides of Perez-polo can be considered to be peptides made by various combinations of deletion, insertion or substitution mutations. Regardless of the peptide homology, any peptide sequence may be

modified via deletion, insertion or substitution mutation to provide any other peptide sequence. Thus, a broad but reasonable interpretation within the scope of the invention is that the Perez-polo sequence is a modified peptide by deletion, insertion or substitution mutation. Moreover, the Perez-polo peptides provide for the recited biological function noted in the claims.

Thus, as J. Regino Perez-Polo teach multiple peptides which effect nerve cells by stimulating growth, cell survival, the promotion of axonal regeneration and synapse formation including peptides derived from nerve growth factor receptor, nerve growth factor and brain derived neurotrophic factor, see in particular Abstract, Background, columns 1-7 and Summary, column 8, the peptides inherently meet the structural and functional limitations of the claims and are therefore anticipatory. The molecules cannot be excluded from applicants generic recitation which includes deletion, insertion and substitution mutations of hNPRAP and thus, the reference teachings reasonably anticipate the claimed invention.

Status of Claims

14. No claims are allowed.

Conclusion

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR

1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 6:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached at (703) 308-4623.

Sharon L. Turner, Ph.D.
May 7, 2002